AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report

Priority Area 10: Obesity

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 11,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas and one cross-cutting area.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COI). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are

sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the potential high impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as potential high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the nine topics for which (1) preliminary phase III data on drug topics and phase II or phase III data on device or procedure topics were available; (2) information was compiled by April 15, 2012, in this priority area; *and* (3) we received six to eight sets of comments from experts between February 2011 and April 26, 2012. (Nineteen topics in this priority area were being tracked in the system as of May 2012.) For purposes of the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present two summaries of two topics (indicated below by an asterisk) that emerged as potential high impact on the basis of experts' comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 10: Obesity

Topic	High Impact Potential
1. *Controlled release phentermine/topiramate (Qnexa) for treatment of obesity	High
2. *EndoBarrier Endoluminal Sleeve for treatment of obesity	Lower range of high impact
3. Full Sense Bariatric Device for treatment of morbid obesity	No high-impact potential at this time
4. Liraglutide (Victoza) for treatment of obesity	No high-impact potential at this time
5. Lorcaserin (Lorgess) for treatment of obesity	No high-impact potential at this time
6. Maestro vagus nerve block system for treatment of morbid obesity	No high-impact potential at this time
7. Methionine aminopeptidase 2 inhibitor (ZGN-433) for treatment of obesity	No high-impact potential at this time
8. Naltrexone and bupropion HCL (Contrave) for treatment of obesity	No high-impact potential at this time
9. Tesofensine for treatment of obesity	No high-impact potential at this time

Discussion

Based on current definitions, individuals with body mass index (BMI) between 25 and 30 kg/m^2 are considered overweight. Individuals with a BMI >30 kg/m^2 are considered obese. Individuals with BMI >35 or >40 kg/m^2 are considered severely obese and morbidly obese, respectively. According to the U.S. Centers for Disease Control and Prevention (CDC), the prevalence of obesity in the United States increased from 15% of adults in 1980 to about 34% of adults in 2006. By 2008, 68% of the population was deemed overweight, with half of that number being categorized as obese. More than 15 million adults have a body mass index >40 kg/m^2 or a BMI of 35 kg/m^2 and comorbidities. CDC

reports that obesity prevalence among children continues to climb, with about a third of all children 19 years of age and younger categorized as overweight or obese.

Obesity is a major contributor to many diseases, including type 2 diabetes mellitus (T2DM), cardiovascular disease, hypertension, and sleep apnea. Obesity also increases the risk of several types of cancer including colorectal, endometrial, esophageal, renal, and postmenopausal breast cancers.

Waist circumference, which measures abdominal fat, predicts obesity-related risk factors for disease. Men with a waist larger than 40 inches and women with a waist measuring more than 35 inches are at increased risk for obesity-related health consequences. Current data suggest that risk of overweight/obesity-related morbidity and mortality increases as BMI increases past 25 kg/m^2. Research indicates that individuals can reduce their risk of obesity-related adverse health conditions by decreasing their total body weight by about 10%.

CDC also reported that researchers calculated that U.S. medical expenditures attributed to obesity totaled about $147 billion in 2008 dollars and stated that taxpayers, through Medicare and Medicaid programs, paid more than half of these costs.

Only one surgical treatment has definitively demonstrated long-term efficacy for morbidly obese patients (gastric bypass surgery), and only one pharmacotherapy is available for long-term treatment of overweight and obesity. The surgery carries significant risks of morbidity and mortality, and the drug therapy has undesired side effects and limited efficacy in achieving sufficient weight loss. Additional treatment options are highly desired. Some new options are in development, but have had a long and sometimes circuitous path to marketing approval.

Concerns over lack of availability of pharmacotherapies approved by the U.S. Food and Drug Administration (FDA) for treating obesity were expressed in September 2011 by the U.S. Congressional Committee on Appropriations. The committee stated "the lack of obesity medications is a significant unmet medical need." This committee directed FDA to develop a pathway by March 30, 2012, to support development of antiobesity treatments. This prompted the FDA to work more closely with manufacturers. In addition, liraglutide (Victoza®, Novo Nordisk a/s, Bagsvaerd, Denmark), an FDA-approved drug for management of T2DM, appears to be of interest for off-label use in treating obesity.

Two drugs considered for this iteration of the High Impact Report but not deemed high impact by experts pose different mechanisms of action. Their approval submissions were initially rejected by FDA. They are lorcaserin (Lorgess®, Arena Pharmaceuticals, Inc., San Diego, CA) and naltrexone HCl/bupropion HCl combination therapy (Contrave®, Orexigen Therapeutics, Inc., La Jolla, CA in collaboration with Takeda Pharmaceutical Co., Ltd., Osaka, Japan). Lorcaserin is an investigational 5-hydroxytryptamine type 2C (5-HT2C) receptor agonist believed to selectively stimulate the 5-HT2C serotonin receptors in the brain, which are involved in controlling appetite and metabolism. In May 2012, the FDA Endocrinologic and Metabolic Drugs Advisory Committee voted 18-4 in favor of recommending approval for lorcaserin. Naltrexone/bupropion drug is a combination oral, sustained-release drug intended to fight the body's tendency to regain weight after weight loss through the combined mechanism of bupropion, which activates the pro-opiomelanocortin neurons in the brain to release a hormone called alpha-MSH, and naltrexone, which inhibits beta-endorphin, a natural opiate believed to increase food intake; a revised new drug application submission is under way. Liraglutide is a synthetic analog of the peptide hormone glucagon-like peptide-1 (GLP-1), which has been shown to suppress appetite and energy intake as well as delay gastric emptying, which may induce a feeling of satiety. A new drug application for treating obesity has not been submitted as of this writing.

Phentermine/Topiramate (Qnexa) for Obesity

- **Key Facts**: Currently, orlistat is the only FDA-approved antiobesity drug available for long-term use in the United States and for use in adolescents. Many patients discontinue treatment

with orlistat because of its unpleasant side effects. New drug treatment options are needed for obese patients seeking medical therapy for weight loss. Phentermine/topiramate (Qnexa®, Vivus, Inc., Mountain View, CA) is a controlled-release formulation of two separate FDA-approved drugs. This drug combination acts on the central nervous system as an appetite suppressant. Phentermine is a central norepinephrine-releasing drug that was approved by FDA in 1959 as an appetite suppressant for short-term (3 months or less) treatment of obesity at a dose of 37.5 mg/day. Topiramate is a gamma aminobutyric acid agonist that was approved by FDA in 1996 for treating epilepsy at a dose of approximately 400 mg/day and has been known to have weight loss as a side effect. Phentermine/topiramate might promote weight loss while avoiding side effects potentially caused by high doses of either drug. In November 2011, FDA accepted a revised new drug application, but in early 2012, it extended the decision date from April 17, 2012, to July 17, 2012. Nonetheless, obesity drug market analysts expressed optimism about its likelihood of approval. Most payers do not cover antiobesity drugs, so patients would likely bear the cost of this drug, unless payers decide to cover it for individuals with comorbidities that could be improved by weight loss achieved with this drug. Out-of-pocket expenses for phentermine/topiramate are projected to be $1,000–$2,000.

- **Key Expert Comments**: Experts generally expressed optimism about this intervention's ability to meet the need of obese patients for a medical solution for moderate weight loss, given the lack of pharmacotherapy interventions and failure of dietary and lifestyle modifications to achieve the needed weight loss among overweight individuals. Experts generally indicated that both patient and clinician acceptance would be high for this drug because the potential to eliminate long-term sequelae of obesity-related diseases is critically important. However, experts opined that the increase in per-patient costs of care might serve as barriers to acceptance for some patients because payers generally do not reimburse for antiobesity drugs.
- **Potential for High Impact**: High

EndoBarrier Endoluminal Sleeve for Excess Weight Loss and/or Treatment of Type 2 Diabetes

- **Key Facts**: Bariatric surgery is the only treatment that has been demonstrated to be effective for morbidly obese patients who do not respond to conservative treatments (e.g., diet, exercise). However, some super-morbidly obese patients are ineligible for surgery because of surgical risks and complications related to their weight. The EndoBarrier® Endoluminal Sleeve (GI Dynamics, Inc., Lexington, MA) device might offer an alternative to such patients. It is a 60-cm impermeable sleeve that allows partially digested food leaving the stomach to move through the gastrointestinal tract without mixing with digestive enzymes or allowing nutrients to be absorbed through the intestinal walls. The device is deployed during a same-day procedure by means of a catheter routed through the esophagus into the stomach and small intestine. There, it is anchored with barbs that penetrate into the muscle wall. The device extends down through parts of the small intestine. The liner can be removed endoscopically using drawstrings that collapse the anchor stent barbs. The device has been on the market in Europe since 2009 and is commercially available in Australia. Results of two European-based trials of the EndoBarrier device were recently published and new results from three studies were reported by the manufacturer in March 2011. The company intends to submit a premarket approval application to FDA, pending outcomes of ongoing trials. At least two large medical device companies have been reported to have invested in the ongoing development in the United Sates. No device/procedure cost information is available at this time.

- **Key Expert Comments**: Overall, experts thought that the EndoBarrier has significant potential to promote moderate, temporary weight loss, which might aid super-morbidly obese patients in achieving the required prebariatric-surgery weight loss and improving diabetes-associated metabolic factors. However, experts were concerned about the treatment's side-effect profile and treatment-discontinuation rate, and they were generally skeptical of whether treatment might truly increase the percentage of patients who could go on to have successful bariatric surgery.
- **Potential for High Impact**: Lower range of high impact

Obesity Interventions

Phentermine/Topiramate (Qnexa) for Treatment of Obesity

The increasing prevalence of overweight and obese populations in the United States has generated a call for novel pharmacologic therapies aimed at weight reduction and maintenance when diet and exercise have failed. However, concerns over potential adverse events associated with antiobesity pharmacotherapies significantly increased the regulatory bar for gaining approval—specifically regarding preapproval safety data and postmarket safety evaluation—set forth by the U.S. Food and Drug Administration (FDA). Currently, orlistat, a pancreatic lipase inhibitor that blocks about one-third of daily fat absorption, is the only FDA-approved antiobesity drug available for long-term use in the United States and for use in adolescents. Many patients discontinue treatment with orlistat because of its unpleasant side effects of oily spotting, flatulence, and fecal urgency. Phentermine-topiramate (Qnexa®, Vivus, Inc., Mountain View, CA) might provide a new option for obese patients seeking medical therapy for weight loss.

Phentermine/topiramate is a controlled-release formulation of two separate FDA-approved drugs. This drug combination acts on the central nervous system as an appetite suppressant.[3] Phentermine is a central norepinephrine-releasing drug that was approved by FDA in 1959 as an appetite suppressant for short-term (3 months or less) treatment of obesity at a dose of 37.5 mg/day.[1,2] Topiramate is a gamma aminobutyric acid agonist that was approved by FDA in 1996 for treating epilepsy at a dose of approximately 400 mg/day and has been known to have weight loss as a side effect.[1,2] Topiramate was studied as a monotherapy for treating obesity; however, dose-dependent neuropsychiatric adverse events precluded further study.[1] By combining the effects of a low dose of each medication in a single treatment, Phentermine/topiramate might promote weight loss while avoiding side effects potentially caused by high doses of either drug. The phentermine plus topiramate combination is administered daily as an oral medication.[3] In late-stage clinical trials, phentermine plus topiramate was administered at three different dose levels: a low dose of phentermine 3.75 mg plus topiramate 23 mg; a middle dose of phentermine 7.5 mg plus topiramate 46 mg; and a high dose of phentermine 15 mg plus topiramate 92 mg.[1]

In 2011, Kushner and colleagues announced results from a phase III clinical trial (SEQUEL) evaluating the safety and efficacy of phentermine/topiramate in 675 obese patients with a body mass index (BMI) between 27 and 45 kg/m^2 and two or more obesity-associated comorbidities. This study is an extension of a phase III, clinical trial (CONQUER). Authors reported the following:

> Patients treated with Qnexa had significant, sustained weight loss compared to those in the placebo group over two years. Average weight loss at week 108 was -9.3% and -10.5%, respectively, for the mid- and top-dose as compared to -1.8% for the placebo group (lease-squares mean ITT-LOCF). Qnexa patients had improved cardiovascular and metabolic risk factors and a decrease in the need for associated medications in comparison with the placebo group. Placebo patients had a three times greater likelihood to progress to type 2 diabetes mellitus (T2DM) compared to subjects receiving top-dose Qnexa and a two times greater likelihood than patients on mid-dose Qnexa.[4,5]

In 2011, Allison and colleagues announced results from a 56-week clinical trial (EQUIP) evaluating the safety and efficacy of phentermine/topiramate in 1,267 morbidly obese patients. The authors reported, "Least-squares (LS) mean weight loss for phentermine/topiramate patients who completed the EQUIP study was 14.4% and 6.7% with top-dose phentermine/topiramate and low-dose phentermine/topiramate, respectively, compared to 2.1% in the placebo group ($p<0.0001$); in the ITT-LOCF analysis, LS mean percent weight loss at week 56 was 10.0% and 5.1% for the top and low dose, respectively, as compared to 1.6% for the placebo group ($p<0.00010$)."[6] The authors also reported that among patients who completed top-dose treatment of phentermine/topiramate, "83.5% lost ≥5%; 67.7% lost ≥10%; and 48.1% lost ≥15% of their baseline weight."[6] Common adverse events

reported in this study were paresthesia (tingling), dysgeusia (taste alteration), and xerostomia (dry mouth).

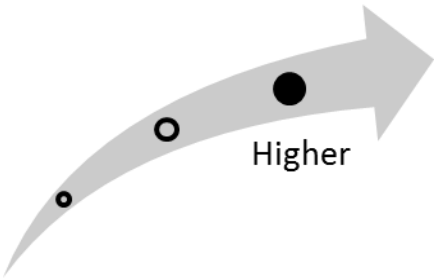
In October 2011, the manufacturer announced the resubmission of its new drug application (NDA) to FDA after a September 2011 meeting with FDA about the next steps.[7] The resubmission presents a new contraindication for "women of childbearing potential." In November 2011, FDA accepted the revised NDA with a decision date set for April 17, 2012.[8] In April 2012, FDA extended the decision date three months to July 17, 2012.

Patients' out-of-pocket costs for the drug have been projected to be $1,000–$2,000 a year.

Clinical Pathway at Point of This Intervention

Patients are usually evaluated for obesity in a primary care setting in which clinicians take height and weight measurements to calculate body mass index (BMI). Individuals with a BMI ≥30 kg/m^2 are classified obese.[9] Obese individuals are screened for other comorbid conditions, such as diabetes and hypothyroidism, that may influence treatment decisions and outcomes.[9] Medication use must also be assessed because some drugs, such as oral contraceptives, certain antipsychotics, and antidiabetes medicines may interfere with weight loss or contribute to excessive weight gain.[10,11] Patients with a BMI ≥30 kg/m^2 or a BMI ≥ 25 kg/m^2 with comorbid obesity-related risk factors or diseases (such as hypertension, dyslipidemia, coronary heart disease, type 2 diabetes mellitus [T2DM], and sleep apnea) may be candidates for drug therapy.[10,11] Drug therapy is typically offered in conjunction with a program of physical activity, nutrition counseling, and behavior management.[10]

Figure 1. Overall High Impact Potential: Phentermine/topiramate for treatment of obesity



Experts commenting on these drugs expressed optimism about their ability to meet the need of obese patients, given the lack of effective interventions for treating obesity. Experts generally indicated that both patient and clinician acceptance would be high for this intervention, because the potential to eliminate long-term sequelae of obesity is critically important. However, potential increase in per-patient costs might serve as barriers to acceptance by some patients. While preliminary results are promising, experts opined that further studies evaluating efficacy and safety are needed. Overall, experts agreed that antiobesity pharmacotherapies could serve as an effective alternative to current interventions for obesity. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on phentermine/topiramate.[12-17]

The experts generally indicated that antiobesity drug therapy has a high potential to meet a significant unmet need in obesity treatment. One clinical expert commented, "There is a significant gap in obesity treatment care for those patients who do not qualify for bariatric surgery but still need help

beyond lifestyle measures alone. Adjuvant medications are limited at present. Additional medications which are safe could help to fill this gap."[14]

Experts generally agreed that phentermine/topiramate has great potential to significantly improve patient health outcomes, with one expert stating, "There have been a number of studies of Qnexa each of which shows a weight loss of between 5 and 15% from baseline. This seems quite significant."[15] Experts remained optimistic about preliminary trial results, although some would like to evaluate long-term, safety trial results before comprehensively assessing this drug's potential health outcomes. However, based on the results from these preliminary studies, experts believe phentermine/topiramate holds strong promise compared with previously and currently investigated antiobesity drugs.

Experts generally agreed that costs associated with antiobesity pharmacotherapies and potential third party payers' unwillingness to cover these therapies might serve as barriers to reducing health disparities related to obesity. A majority of experts agreed the potential for an obesity drug intervention would not significantly disrupt the current health care delivery infrastructure. Several experts opined that antiobesity pharmacotherapies might reduce the need for bariatric surgery in some patients, thus disrupting the current health care model for this patient population.

Experts generally agreed that the potential for clinician and patient acceptance of an effective antiobesity medication is high. While several experts mentioned the uncertainty of long-term adverse events as a potential barrier to patient acceptance of antiobesity pharmacotherapies, one expert opined that patients would acceptingly adopt "a pill, with minimal side effects, and a potential for a 10% weight loss."[15]

Several experts highlighted the fact that antiobesity pharmacotherapy is typically not covered by third-party payers and expected patients to have to bear the costs out of pocket. Although out-of-pocket expenses for phentermine/topiramate are estimated at $1,000–$2,000, several experts believe the potential health outcomes far outweigh the financial costs. A majority of experts thought that reducing or eliminating long-term complications from obesity might ultimately reduce per-patient costs over time. Several experts indicated that initial costs of using these pharmacotherapies might be less costly than undergoing bariatric surgery or other antiobesity surgical interventions. Overall, experts opined that this intervention has high potential to significantly impact this patient population.

EndoBarrier Endoluminal Sleeve for Excess Weight Loss and Treatment of Type 2 Diabetes

Bariatric surgery is the only treatment that has been demonstrated to be effective for morbidly obese patients who do not respond to conservative treatments (e.g., diet, exercise). However, some super-morbidly obese patients who might otherwise benefit from bariatric surgery are ineligible because of surgical risks and limitations posed by their large size, weight, and thickness of adipose tissue. Additionally, preoperative weight loss is widely recognized as correlating with improved outcomes and reduction of diabetes-related risks in all bariatric surgery patients. Therefore, a need exists for minimally invasive treatments that could enable super-obese patients to lose 5% to 10% of their excess body weight.

EndoBarrier Luminal Sleeve (GI Dynamics, Inc., Lexington, MA) is intended to address this need. The device is a 60-cm impermeable sleeve that allows chyme (partially digested food leaving the stomach) to move through the gastrointestinal (GI) tract without mixing with digestive enzymes or allowing nutrients to be absorbed through the intestinal walls.[18] It is inserted under general anesthesia using dynamic fluoroscopic imaging; however, it may be possible to implant the device with the patient under conscious sedation in the future.[18] When implanted, the EndoBarrier is anchored within the duodenal bulb (small area of the small intestine just outside of the stomach) by a 5.5-cm nitinol (alloy of nickel and titanium), self-expanding stent with barbs that penetrate into the muscular wall of the intestine.[18] The sleeve extends down through parts of the small intestine (duodenum and proximal jejunum) and is purported to mimic the effects of GI bypass surgery.[18] The device is intended to remain in place for 12–24 weeks, during which time the patient is on a liquid diet supplemented with multivitamins and proton pump inhibitors to control acid reflux.[18-20] When weight loss is achieved, the device is removed endoscopically by collapsing the nitinol stent and withdrawing the device from the stomach up through the esophagus.[18]

The EndoBarrier was cleared in 2009 for use in Europe. Results of two European-based trials of the EndoBarrier device were published in 2010,[18,21] and updated results from three studies were reported by the company in March 2011.[22] In July 2011, the system was approved by the Australian Therapeutic Goods Administration for inclusion in its therapeutic goods registry for treating T2DM and obesity for up to 12 months.[23] The company has not yet submitted a premarket approval application to FDA, pending outcomes of ongoing investigational device exemption trials. At least two large device companies reportedly have invested in the device's development in the United States.

In one European-based trial, 30 patients with a mean BMI of 48.9 kg/m^2 underwent EndoBarrier implantation in conjunction with dietary restriction and were compared with 11 patients in a control group with a mean BMI of 47.4 kg/m^2 who underwent dietary restriction alone.[18] Researchers reported that implantation was successful in 26 of 30 patients; however, the device was removed after 12 weeks in 4 patients because of device migration, dislocation of the device anchor, sleeve obstruction, or continuous epigastric pain.[18] Researchers reported that for patients completing the 12-week study, mean excess weight loss was 19.0% in the EndoBarrier-treated group versus 6.9% in the control group ($p<0.002$).[18] Adverse events were reported in 100% of patients in this study. The majority of these events were reported as abdominal pain and nausea during the first week after implantation; however, 23% of patients were reported to have vomiting during the first week after implantation, 50% of patients were reported to have pseudopolyp formation postexplantation, and 38.5% of patients were reported to have implant-site inflammation postexplantation.[18]

In a second European trial, EndoBarrier implantation was attempted on 27 patients whose outcomes were compared with 29 patients who underwent a sham implantation.[21] Researchers reported that of 21 patients in whom EndoBarrier was successfully implanted, 8 terminated treatment before the full 12-week treatment because of GI bleeding (n=3), abdominal pain (n=2), nausea and vomiting

(n=2), or an illness unrelated to treatment (n=1).[21] Thirteen EndoBarrier implanted patients and 24 sham patients completed the 12-week study with reported excess weight losses of 11.9% and 2.7% for the EndoBarrier and sham arms, respectively.[21]

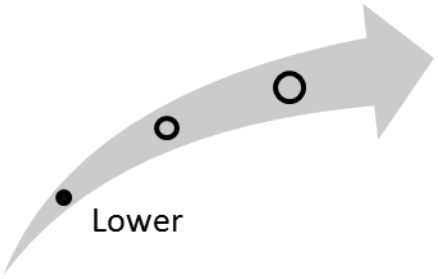
Results from three trials were reported in a company press release on presentations given at the Second World Congress on Interventional Therapies for Type 2 Diabetes in March 2011, in Parkstad Heerlen, The Netherlands.[22] One trial was on EndoBarrier's effects on two hormones (gut peptides glucagon-like peptide-1 [GLP-1] and peptide YY [PYY]) and other diabetes measures. Jan Willem Greve, M.D., Ph.D., of the Gastrointestinal and Bariatric Surgery practice, Parkstad Heerlen, reported that "EndoBarrier treatment offered rapid and long-lasting improvement in diabetes, and for the first time, demonstrated beneficial hormonal effects similar to surgical interventions such as Roux-en-Y gastric bypass." The study reported results of a study of 17 obese patients with T2DM who received EndoBarrier for 24 weeks. Glycated hemoglobin A_{1c} (HbA_{1c}), glucose, insulin, GLP-1, and PYY were assessed. Patients were reported to have had a rapid increase and sustained insulin sensitivity, increased levels of both PYY and GLP-1 at 1 week after implantation, a mean excess weight loss of 29.8%, reduction of HbA_{1c} from 8.4% at baseline to 7.0% after 6 months, and reduced intake of antidiabetic medications in 16 of 17 patients.[22]

Two other clinical trials reported on in a company press release about the meeting were cited as evidence by the manufacturer that the EndoBarrier may be a candidate for the primary therapy of T2DM and obesity.[22] E.G. Moura, M.D., Ph.D., director of endoscopy, Hospital das Clinicas, University of São Paulo, Brazil, evaluated the EndoBarrier in 22 patients with T2DM for 1 year. Patients' HbA_{1c} declined from 8.9% at baseline to 6.6% ($p<0.0001$); absolute weight loss was 20.2 kg (44 lb; $p<0.0001$), or 39% excess weight loss ($p<0.0001$). Also, metabolic functions including levels of insulin, cholesterol, low-density lipoprotein, and triglycerides levels normalized at 1 year. Alex Escalona, M.D., Department of Digestive Surgery, Pontificia Universidad Católica de Chile, Santiago, Chile, reported on weight loss and cardiometabolic factors in 46 obese patients 1 year after implantation. Patients achieved 20.0% total body weight loss (22.8 kg/50 lb) or 46.4% excess weight loss ($p<0.0001$), and total cholesterol and diastolic blood pressure declined significantly. A subset of six patients in the trial with T2DM achieved a mean HbA_{1c} reduction of 1.4% ($p=0.05$; 7.9% at baseline to 6.5%).

Clinical Pathway at Point of This Intervention

The National Institutes of Health's Panel on Weight Loss recommended that morbidly obese patients lose 10% of their excess body weight before bariatric surgery to help reduce surgical risks and postoperative complications.[24] However, currently available preoperative weight loss methods have demonstrated suboptimal success in morbidly obese patients. Losing weight through diet and exercise alone has often not been successful for this patient population.[24] Therefore, physicians may also recommend weight-loss medication, although that option is limited to only one approved drug.[24] Patients and clinicians would welcome the availability of other options for promoting preoperative weight loss in patients who have failed to lose weight using conservative treatment options.

Figure 2. Overall High Impact Potential: EndoBarrier endoluminal sleeve for excess weight loss



Overall, experts commenting on this intervention thought that EndoBarrier appears to have potential to promote moderate, temporary weight loss, which could aid super-morbidly obese patients in achieving the required weight to undergo bariatric surgery and could also aid in improving diabetes-associated metabolic factors. The potential was tempered by experts' significant concerns about reported adverse events. They were also generally skeptical about whether treatment would truly increase the percentage of patients who would become eligible to undergo successful bariatric surgery. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this topic.[25-30] Experts agreed that a significant unmet need exists for treatments that could aid morbidly obese patients in losing weight to become eligible for bariatric surgery or in reducing the risks associated with diabetes, citing the increasing prevalence of obesity in the United States and the current lack of effective noninvasive weight-loss treatments for this population. Additionally, experts agreed that the idea of inhibiting absorption in the intestine using an explantable impermeable barrier seems logical and noted that preliminary data on weight loss seems promising. However, multiple experts also noted the significant reported side effects and adverse events and the discontinuation rate, which they believe to be significant adverse factors. Additionally, several of these experts raised the concern that for a temporary treatment such as EndoBarrier to ultimately be effective, patients would need to transition to successful definitive bariatric surgery and that data on this outcome have not been reported. Lastly, one expert with a health systems background suggested that patients who would need to resort to EndoBarrier treatment to achieve prebariatric-surgery weight loss might not be fully committed to the lifestyle changes required for successful subsequent bariatric surgery outcomes.

Regardless of the potential treatment efficacy, the EndoBarrier appears to have significant potential to increase scientific understanding of the GI system and the mechanism of action of bariatric surgeries, one clinical and one research expert commented; however, these observations may be more applicable to the potential of the device to control T2DM.

Most of the experts providing comments did not see potential for a shift in care setting, but one clinical expert and one researcher observed that bariatric procedures are generally surgical procedures whereas the EndoBarrier would likely be implanted in an endoscopy suite, which could involve capital equipment purchases for facilities that do not currently employ endoscopy in their bariatric practices. Experts also suggested that the intervention could shift the type of specialist providing bariatric services from surgeons to GI physicians accustomed to doing endoscopy. If bariatric surgeons decide to perform the endoscopic procedure, experts opined, they would likely need training.

The expert opinions regarding treatment costs and reimbursement of EndoBarrier were highly variable. Several experts suggested that a temporary procedure such as the EndoBarrier would be

unlikely to be reimbursed by third-party payers unless long-term outcomes on metabolic outcomes and transition to gastric bypass surgery were reported. From a broader perspective, multiple experts noted that if EndoBarrier leads to patients undergoing successful bariatric surgery, the treatment could be cost effective because of a reduction in the costs associated with treating the effects of morbid obesity and diabetes.

As for whether patients were likely to opt for the EndoBarrier system, one clinical expert suggested that patients would be more likely to seek less invasive and cheaper alternatives for preoperative weight loss. Conversely, multiple experts noted that patients who would opt for EndoBarrier treatment would likely have exhausted conservative options. While multiple experts suggested that the potential for adverse side effects could deter patients from opting for EndoBarrier treatment, others noted that the target patient population would already be intending to undergo bariatric surgery, which carries significant risks, and such patients can have a high tolerance for risk.

Experts did not envision many barriers to physician adoption of EndoBarrier treatment, provided it is shown to be sufficiently safe and effective. Several experts noted some training would be involved in learning the implantation procedure, but did not think it would be a significant barrier.

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